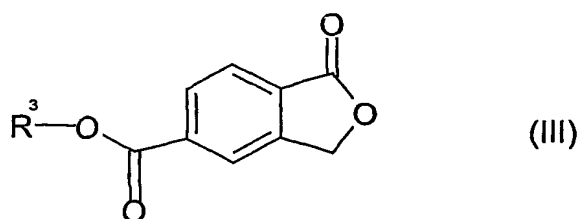


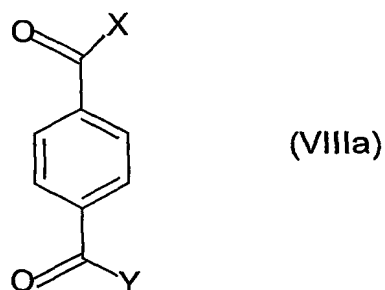
Claims

1. A method for preparing an alkoxycarbonylphtalide of formula (III)



comprising:

- 5 (a) reacting a compound of formula (VIIIa) with a formaldehyde and oleum; and

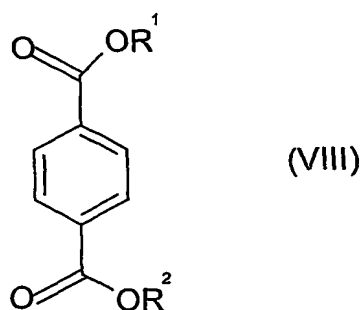


- (b) addition of an alcohol R^3 -OH to the reaction of step (a);

wherein X and Y of formula (VIIIa) may be selected independently from the group consisting of: OR^1 , OR^2 , a halogen (such as Cl, Br, I), and NR; wherein R, R^1 and R^2 are independently H or a C_{1-6} -alkyl; and R^3 is a C_{1-6} -alkyl or phenyl.

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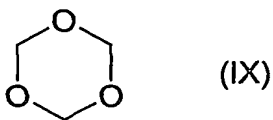
2. A method according to claim 1 wherein the compound of formula (VIIIa) is a compound of formula (VIII)



wherein R^1 and R^2 are selected independently from H and C_{1-6} -alkyl.

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3. The method of claim 1 or 2, wherein the formaldehyde is 1,3,5-trioxane of formula IX.



4. The method of claim 1 or 2, wherein the formaldehyde is paraformaldehyde.

5. The method of any of the preceding claims, wherein R^3 is a C_{1-6} -alkyl.

6. The method of any of the preceding claims, wherein the C_{1-6} -alkyl is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert-butyl, n-pentyl and n-hexyl.

7. The method of any of claims 1-4, wherein R^3 is ethyl or n-butyl.

8. The method of any of claims 1-4, wherein R^3 is a C_4 -alkyl, preferably n-butyl.

9. The method of the any of claims 1-6, with the proviso that R^3 is not methyl.

10. The method of the any of claims 1-6, with the proviso that R^3 is not ethyl.

11. The method of the any of claims 1-6, wherein R^3 a C_{3-6} -alkyl; or R^3 is a C_{4-6} -alkyl.

12. The method of any of the preceding claims, wherein R^1 and R^2 are selected independently from the group consisting of hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert-butyl, n-pentyl and n-hexyl.

13. The method of claim 12, wherein R^1 and R^2 are selected independently from the group consisting of hydrogen, methyl, ethyl and n-butyl.

14. The method of any of the preceding claims, wherein at least one of R^1 and R^2 is not H.

15. The method of any of claims 1-13, wherein R^1 is identical to R^2 .

16. The method of claim 15, wherein R^1 and R^2 are identically methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert-butyl, n-pentyl or n-hexyl.

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17. The method of claim 15, wherein R^1 and R^2 are identically methyl, ethyl or n-butyl.

18. The method of any of claims 1-13, wherein R^1 and R^2 are H.

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19. The method of any of claims 1-13, with the proviso that if R^1 and R^2 are H, then R^3 is not methyl or ethyl.

20. The method of any of claims 1-4, wherein R^1 and R^2 are H and R^3 is n-butyl; R^1 and R^2 are methyl and R^3 is n-butyl; or R^1 and R^2 are ethyl and R^3 is n-butyl.

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21. The method of any of the preceding claims, wherein in step (a) is used 1-3 equivalents of the formaldehyde per equivalent of the compound of formula (VIII).

22. The method of claim 20, wherein there in step (a) is used 1-2 equivalents, preferably 1-1,5 equivalents of the formaldehyde per equivalent of the compound of formula (VIII).

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23. The method of any of the preceding claims, wherein there in step (a) is used 1-8 l oleum per kg of formula (VIII), such as 1.5-6 l/Kg; 1.5-4 l/Kg; 1.5-3.5 l/kg, preferably in the range of 1.5-3.5 l oleum per kg of formula (VIII).

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24. The method of claim 23, wherein there in step (a) is used 1.5-2.5l oleum per kg of formula (VIII).

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25. The method of any of the preceding claims, wherein the oleum in step (a) contains 18-65% SO_3 .

26. The method of any of claims 1-24, wherein in step (a) the oleum contains 16-20% SO₃, e.g. 16-18% SO₃.

27. The method of any of the preceding claims, wherein the reaction in step (a) is performed for at least 1 hour, preferably in the range of 1-24 hours, e.g. 2-18 hours, 2-10 hours, and preferably 2-5 hours.

28. The method of any of the preceding claims, wherein step (a) is performed at a temperature in the range of 115 °C – 175 °C.

29. The method of any of claims 1-27, wherein step (a) is performed at a temperature in the range of 115 °C – 150 °C.

30. The method of any of claims 1-27, wherein step (a) is performed at a temperature in the range of 150 °C – 175 °C.

31. The method of any of claims 28-30, wherein the reaction in step (a) is performed at said temperature for a period of at least 1 hour, preferably in the range of 1-24 hours, e.g. 2-18 hours, 2-10 hours, and preferably 2-5 hours.

32. The method of any of the preceding claims, wherein in step (a) a mixture of the compound of formula (VIII) in oleum is heated to a temperature as defined in any of claims 28-30 before the addition of formaldehyde, preferably paraformaldehyde in oleum.

33. The method of any of the preceding claims, wherein step (b) is performed at a temperature below the boiling point of the alcohol.

34. The method of claim 30, of claim 31 referring to claim 30, or of claim 32 referring to claim 30 wherein the oleum contains 16-19% SO₃.

35. The method of any of the preceding claims, said method comprising collecting the alkoxycarbonylphtalide by filtration.

36. The method of any of the preceding claims, said method comprising purification of the alkoxycarbonylphtalide by addition of an organic solvent and aqueous solvent, preferably water, thereby extracting the alkoxycarbonylphtalide into the organic phase.

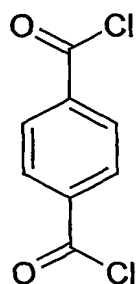
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37. The method of claim 36, said method comprising collecting by filtration the extracted alkoxycarbonylphtalide.

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38. The method of claim 35 or 37, said method comprising drying the collected alkoxycarbonylphtalide.

39. A method of claim 1 or any of claims 3-11 referring to claim 1 or any of claims 21-38 referring to claim 1, wherein the compound of formula (VIIIa) is terephthaloyl dichloride of formula (B)



(B)

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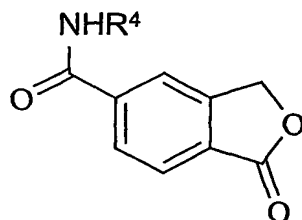
40. The method of claim 39, wherein the reaction mixture of step (a) is cooled down to a temperature of less than 40 °C, such as less than 35 °C, less than 30 °C, e.g. in the range 15 - 30 °C, such as 18 - 30 °C or 18 - 25 °C, preferably at room temperature, before the addition of the alcohol.

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41. The method of claim 40, wherein during step (b) the temperature is in the range of 75 - 110 °C, preferably in the range of 80 °C and 100 °C.

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42. The method as defined in any of claims 1-41, further comprising converting the alkoxycarbonylphtalide resulting from said method to the amide of formula (IV), wherein R⁴ is H or C₁₋₆-alkyl.

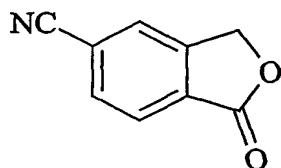


(IV)

43. The method of claim 42, wherein the alkoxycarbonylphtalide is converted to the amid of formula (IV) by amidation with ammonia or an C_{1-6} -alkylamine.

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44. The method of claim 42 or 43, wherein the amide of Formula (IV) is reacted with a dehydrating agent, e.g. SOCl_2 , thereby obtaining 5-cyanophthalide having the Formula (V).



(V)

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45. A method for the synthesis of 5-cyanophthalide from a alkoxycarbonylphtalide of formula (III) as defined in claim 1, which alkoxycarbonylphtalide has been prepared by a method as defined in any of claims 1-41.

15 46. A method for the synthesis of 5-cyanophthalide comprising the method for preparing an alkoxycarbonylphtalide of formula (III) according to any of claims 1-41.

47. A method for the synthesis of citalopram or escitalopram from a alkoxycarbonylphtalide of formula (III) as defined in claim 1, wherein the
20 alkoxycarbonylphtalide has been prepared by a method as defined in any of claims 1-41.

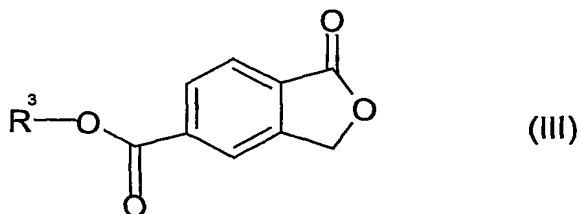
48. A method for the synthesis of citalopram or escitalopram comprising a method preparing a alkoxycarbonylphtalide of formula (III) according to any of claims 1-41.

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49. A method for the synthesis of citalopram or escitalopram comprising the method for the synthesis of 5-cyanophthalide of any of claims 45-46.

50. A method for preparing an intermediate suitable for the synthesis of citalopram or escitalopram, said method comprising the steps of:

(i) preparing a alkoxycarbonylphtalide of formula (III),

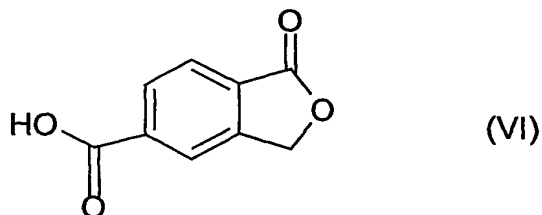


wherein R^3 is a C_3 - C_6 -alkyl

(ii) subjecting the alkoxycarbonylphtalide of formula (III) to an isolation procedure, said isolation procedure preferably comprising a filtration step.

51. The method of claim 50, wherein R^3 is a C_4 -alkyl, preferably n-butyl.

52. The method of claim 50 or 51, wherein the alkoxycarbonylphtalide in step (i) is prepared by a method as defined in any of claims 1-41; or by a method comprising the step of esterification of 5-carboxyphthalide of formula (VI).



53. The method of claim 52, wherein the 5-carboxyphthalide of formula (VI) is prepared by a method comprising:

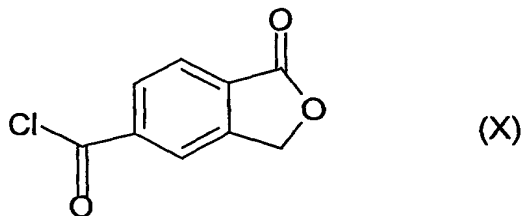
- (a) reacting the compound of formula (VIII) as defined in claim 1 with a formaldehyde and oleum; and
- (b) addition of an aqueous solution, preferably water.

54. The method of claim 53, wherein R^1 and R^2 in the compound of formula (VIII) are H.

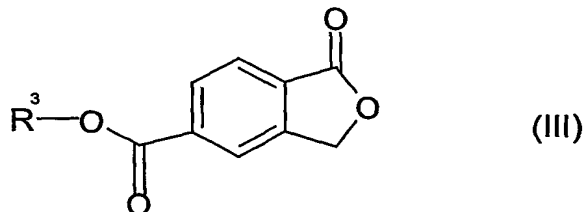
55. The method of claim 54, wherein the prepared 5-carboxyphthalide is not dried before the esterification.

5 56. The method of any of claims 52-55, wherein the esterification in step (c) is obtained:

- (i) by treatment of 5-carboxyphthalide with an alcohol R^3 -OH in the presence of an acid, wherein R^3 is as defined in claim 50 or 51; or
 - (ii) from the corresponding acid chloride of formula (X) by reaction with an
- 10 alcohol R^3 -OH, wherein R^3 is as defined in claim 50 or 51.



57. An alkoxycarbonylphthalide of formula (III),



15 wherein R^3 is a C_{1-6} -alkyl or phenyl.

58. The alkoxycarbonylphthalide of claim 57, wherein R^3 is as defined in any of claims 5-11.